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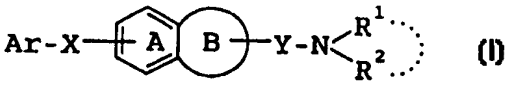
(54) Title: AMINE COMPOUNDS, THEIR PRODUCTION AND USE AS AMYLOID–BETA PRODUCTION INHIBITORS



(I)

(57) Abstract

A compound of formula (I) wherein Ar is an aromatic ring assembly group which may be substituted or a fused aromatic group which may be substituted; X is (i) a bond, (ii) –S–, –SO– or –SO_2–, (iii) C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene, etc., (iv) –CO–O– or (v) –(CH_2)p–x^1–, –(CH_2)p–X^1–(CH_2)q–, –(CH_2)r–CO–X^1–, –SO_2–NR^8– or –(CH_2)r–SO_2–NR^8– wherein X^1 is O or NR^8, R^8 is H, a hydrocarbon group which may be substituted or an acyl, p is 0 to 5, q is 1 to 5, p+q is 1 to 5, and r is 1 to 4; Y is a divalent C_{1-6} aliphatic hydrocarbon group optionally containing O or S, which may be substituted; R^1 and R^2 each is H or a lower alkyl which may be substituted, or R^1 and R^2 form an N–containing heterocyclic ring which may be substituted; Ring A is a benzene ring which may be further substituted; and Ring B is a 4– to 8–membered ring which may be further substituted, or a salt thereof has the effect of inhibiting amyloid–β protein production and/or secretion and is useful as a pharmaceutical composition for preventing and/or treating the neurodegenerative disease, etc.

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DESCRIPTION

AMINE COMPOUNDS, THEIR PRODUCTION AND USE AS AMYLOID-BETA PRODUCTION INHIBITORS

TECHNICAL FIELD

The present invention relates to an amine compound having an excellent effect of inhibiting production and/or secretion of amyloid-β protein, a production and use thereof. Especially, it is effective for preventing and/or treating, for example, neurodegenerative diseases, amyloid angiopathy, neurological disorders caused by cerebrovascular disorders, and so forth.

BACKGROUND ART

Alzheimer's disease is a neurodegenerative disease, which is characterized by the degeneration and loss of neuronal cells accompanied by the formation of senile plaques and neurofibrillary tangles. Senile plaque that is the most characteristic in Alzheimer's disease consist of essentially amyloid-β protein (hereinafter referred to as Aβ) [see Biochem. Biophys. Res. Commun., 122, 1311 (1984)] and other intracerebral components. It is known that Aβ comprised of 40 or 42 amino acids (hereinafter referred to as $A\beta_{1-40}$ and $A\beta_{1-42}$, respectively) is toxic to neurons and induces neurofibrillary changes.

Some patients with familial Alzheimer's disease are known to have APP (amyloid precursor protein) gene mutation, and it is well known that the cells transfected with such mutated gene produce and secrete an increased amount of Aβ [for example, see Nature, 360, 672 (1992); Science, 259, 514 (1993); Science, 264, 1336 (1994), etc.].

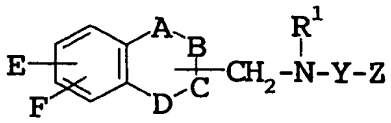
Based on the information, medicines which inhibit production and/or secretion are useful for preventing and/or treating diseases caused by Aβ (e.g., Alzheimer's disease, Down's syndrome, etc).

Alternatively, secreted form of amyloid precursor protein (sAPP) is reported to have neurotrophic factor like property (Neuron, 10, 243-254,1993). As neurotrophic factor like property, 1) survival and preserving effect to the neuronal cell; 2) stimulating the synapse formation; 3) protection of neuronal cell death; and 4) long term potentiation in hippocampus are given as examples. By the above-mentioned property, drugs which stimulate the sAPP secretion are also useful in preventing and treating 1) neurodegenerative diseases such as dementia (e.g., senile dementia, amnesia, etc.), Alzheimer's disease, Down's syndrome, Parkinson's disease, Creutzfeldt-Jacob disease, amyotrophic sclerosis on lateral fasciculus, Huntington's disease, multiple sclerosis, etc., 2) neurological disorders involved in cerebrovascular disorders (e.g., cerebral infarction, encephalorrhagia, etc.), a head injury or an injury of spinal cord, and so forth.

EP-A-652009 discloses peptide derivatives which is a protease inhibitor exhibiting an Aβ production inhibiting effect in *in vitro* experiments using cell lines.

On the other hand, the following bicyclic amine compounds are known.

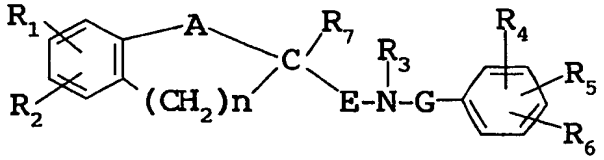
1) JP-A-2-96552 (USP 5,137,901) discloses a compound of the formula:



wherein Y represents a straight-chain or branched,

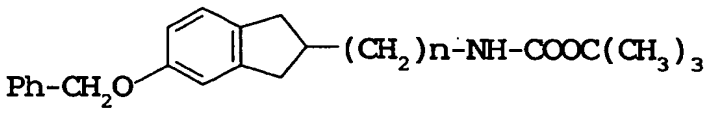
substituted or unsubstituted alkylene chain having up to 6 carbon atoms; Z represents a group of the formula: $-NR^2R^3$, $-OR^4$, or the like; R^2 and R^3 are identical or different and represent hydrogen, alkyl, alkenyl or cycloalkyl, or represent aryl which may be substituted by halogen, etc.; R^4 represents hydrogen, alkyl, alkenyl, or the like; R^1 represents hydrogen, alkyl, aralkyl, heteroarylalkyl or a group of the formula: $-(Y^1-Z^1)$ in which Y^1 and Z^1 are identical or different and have the same meanings as Y and Z; A and D each represents a group of the formula: $-CH_2$, O, S or NR^{13}, or the moiety of -CH or N of a double bond C=C or C=NH, with the proviso that either only A or only D represents oxygen, sulfur or $N-R^{13}$; R^{13} represents hydrogen, alkyl, alkoxy, acyl, alkoxycarbonyl or alkylsulfonyl; B represents a group of the formula: $-CH_2$ or $\geqslant CH$ or the moiety of -CH or N of a double bond C=C or C=N; C represents a group of the formula: $\geqslant CH$, or the moiety of C of a double bond C=C or C=N; E and F are identical or different and each represents hydrogen, alkyl, alkoxy, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy or a group of the formula: $-CONR^2R^3$ in which R^2 and R^3 have the same meanings as above, or E and F together form a substituted or unsubstituted carbocycle having 6 carbon atoms, which is agonist, partial agonist and antagonist on the serotonin receptors and is suitable for the treatment of central nervous system disorders, etc.

2) JP-A-63-77842 discloses a compound of the formula:



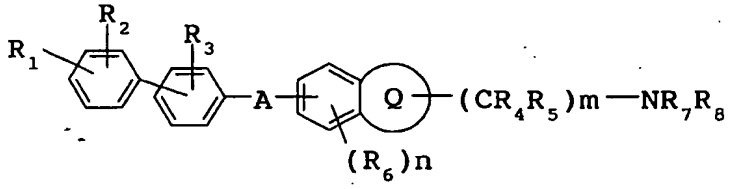
wherein n represents 1 or 2; A represents a carbonyl while R_7 is hydrogen, or A represents a group of the formula: $-CHR_8-$ wherein R_8 represents hydrogen, alkanoyloxy or alkoxycarbonyl, while R_7 is hydrogen or R_7 and R_8 together form another bond; E represents a straight-chain alkylene which has 3 or 4 carbon atoms and may be substituted by an alkyl; G represents a straight-chain alkylene which has 2 to 5 carbon atoms and may be substituted by an alkyl; R_1 represents hydrogen, trifluoromethyl, nitro, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy or phenylalkoxy; R_2 represents hydrogen, halogen atoms, hydroxy, alkoxy, phenylalkoxy or alkyl; or R_1 and R_2 together form an alkylenedioxy having 1 or 2 carbon atoms; R_3 represents hydrogen, alkenyl or alkyl having 3 to 5 carbon atoms; R_4 represents hydrogen, halogen atoms, alkyl, or the like; R_5 represents hydrogen, halogen atoms, alkyl, or the like; and R_6 represents hydrogen, halogen atoms, alkyl, or the like, which is suitable for the treatment of sinus tachycardia and also for the prevention and treatment of ischemic heart disease because of its pharmacological action, decrease in the heart rate and oxygen demand of the heart.

3) WO 92/15558 discloses a compound of the formula:



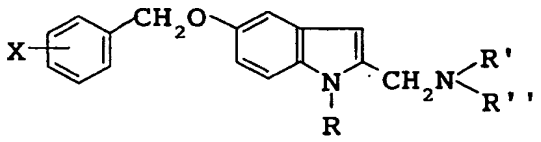
wherein n represents an integer of 1 to 4, which is an intermediate of a compound having a thromboxane A_2 antagonistic effect.

4) WO 95/32967 discloses amide derivatives of the formula:



wherein A is CONR where R is hydrogen or C_{1-6} alkyl; Q is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur; R_1 is hydrogen, halogen, etc.; R_2 and R_3 are independently hydrogen, halogen, etc.; R_4 and R_5 are independently hydrogen or C_{1-6} alkyl; R_6 is halogen, hydroxy, etc.; R_7 and R_8 are independently hydrogen, C_{1-6} alkyl, aralkyl, or together with the nitrogen atom to which they are attached from an optionally substituted 5 to 7-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen or sulphur; m is 0 to 4; and n is 0, 1 or 2, which has $5HT_{1D}$ receptor antagonist activity and is useful for the treatment of various CNS disorders.

5) EP-A-754455 discloses a pharmaceutical compositions for the therapeutic application as neuroprotectors in Parkinson's and Alzheimer's diseases containing a compound of the formula:



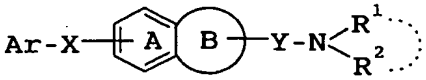
wherein X is H, halogen, alkoxy, alkyl, alkylthio, aryl, aryloxy; R is H, CH_3 or other aliphatic, alicyclic or aryl radicals; R' is H, CH_3 or other aliphatic or alicyclic C_1-C_3 radicals, or an aryl or arylalkyl, or a radical the same as those indicated for R''; and R'' is H, CH_3 or other aliphatic or alicyclic C_1-C_3 radicals, or an aryl or arylalkyl, or an acetylene or allene

group, being potent selective monoamine oxydase B inhibitors.

The conventional Aβ production inhibitors for the treatment of Alzheimer's disease are problematic in their oral absorbability, stability, etc. and are therefore unsatisfactory as medicines. It is desired to develop a compound which is different from the known compounds mentioned above in its chemical structure and which have an excellent inhibitory effect on Aβ production and/or secretion and is therefore satisfactorily used in medicines.

DISCLOSURE OF INVENTION

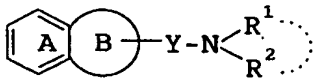
We, the present inventors have studied various compounds having an inhibitory effect on Aβ production and/or secretion and, as a result, have succeeded in, for the first time, the production of novel a compound of the formula:



(I)

wherein Ar represents an aromatic ring assembly group which may be substituted or a fused aromatic group which may be substituted;
X represents (i) a bond, (ii) -S-, -SO- or $-SO_2-$, (iii) a C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of oxo and C_{1-6} alkyl, (iv) -CO-O- or (v) a group of the formula: $-(CH_2)p-X^1-$, $-(CH_2)p-X^1-(CH_2)q-$, $-(CH_2)r-CO-X^1-$, $-SO_2-NR^8-$ or $-(CH_2)r-SO_2-NR^8-$ wherein X^1 represents O (oxygen atom) or NR^8, R^8 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl, p represents an integer of 0 to 5, q represents an integer of 1 to 5,

p+q is an integer of 1 to 5, and r represents an integer of 1 to 4;
Y represents a divalent C_{1-6} aliphatic hydrocarbon group which may contain an oxygen atom or a sulfur atom and may be substituted;
R^1 and R^2 each represents a hydrogen atom or a lower alkyl which may be substituted, or
R^1 and R^2 form, taken together with the adjacent nitrogen atom, a nitrogen-containing heterocyclic ring which may be substituted;
Ring A represents a benzene ring which may be further substituted apart from the group of the formula: -X-Ar wherein each symbol is as defined above; and
Ring B represents a 4- to 8-membered ring which may be further substituted apart from the group of the formula: $-Y-NR^1R^2$ wherein each symbol is as defined above;
provided that, when the fused ring to be formed by Ring A and Ring B is an indole ring, the group of the formula: -X-Ar wherein each symbol is as defined above is substituted on 4-, 6- or 7-position of the indole ring, or a salt thereof [hereinafter sometimes referred to as compound (I)], which is characterized by the chemical structure in that the benzene ring A of the skeleton of the formula:



wherein the symbols have the same meanings as above, is substituted by the group of the formula: -X-Ar wherein the symbols have the same meanings as above. We have found for the first time that compound (I), being based on its specific chemical structure, has an unexpected, excellent inhibitory effect on Aβ production and/or secretion, that a compound of the formula: